J. Pharm. Pharmacol. 1998, 50 (Supplement): 56

The physico-chemical basis of enhanced drug absorption: calorimetric studies of drug/surfactant interactions

R. PATEL, G. BUCKTON, D. A. RAWLINS* AND D. E. STOREY†

*The Centre for Materials Science, The School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, *Merck Sharp and Dohme, Hertford Road, Hoddesdon, Hertfordshire, and †Merck & Co Inc., Westpoint PA 19486, USA*

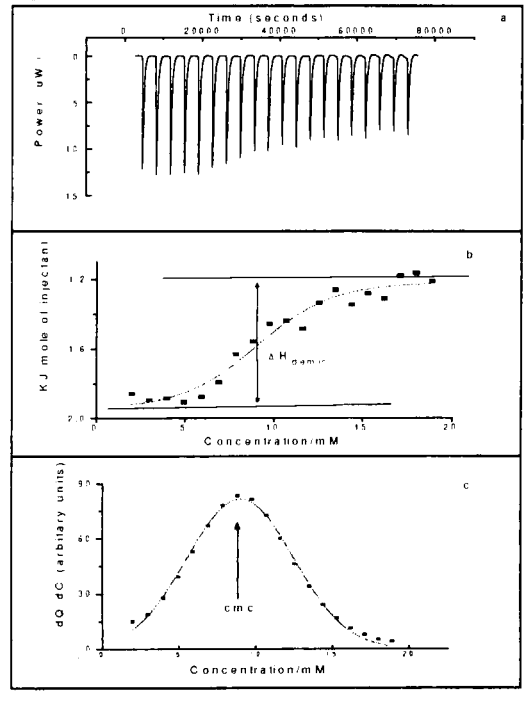
It is known that the absorption of drugs with low aqueous solubility from the gastro-intestinal tract is enhanced by the presence of surfactants, however the mechanism of enhancement remains unclear. Whilst the in vivo situation remains difficult to model, it is clear that an improved understanding of how drugs interact with surfactants will assist in understanding how absorption is enhanced.

In this study we explore the interaction of a poorly soluble drug, simvastatin, with sodium deoxycholate (SDCH), and sodium dodecyl sulphate. Titration isothermal microcalorimetry (Thermometric) was used to accurately measure the heats of dilution, from which the cmc was obtained. The experiments involved consecutively injecting concentrated surfactant into a calorimetric vessel containing water or a saturated solution of simvastatin. Initially the heat associated with each injection, after correcting for blanks, was due to the break up of micelles to give monomers (giving the enthalpy of demicellisation). Once the final concentration in the vessel exceeded the cmc the heat change on further injections was smaller as the micelles did not dissociate but were simply diluted. This was then repeated in the presence of drug solution. Differences between the dilution of surfactant solution in water and into the drug solution can be ascribed to surfactant-drug interactions.

The solubility of the drug was also measured in a range of surfactant concentrations in water. Using this data and the aggregation number of the micelles, it was possible to calculate the number of drug molecules solubilised per micelle.

A typical titration calorimetry result is shown in Fig 1 for SDCH from which it can be seen that the cmc is 9mM. It was found that the cmc shifted to 12mM when simvastatin was present. This elevation of the cmc indicates a stabilising of the free surfactant in water, presumably as loosely associated drug-SDCH aggregates. The mean number of molecules of simvastatin per micelle was calculated to be 0.3, which shows that the extent of solubilisation is low and that this surfactant cannot enhance absorption by solubilisation.

Figure 1. a) heat flow. b) reaction enthalpy. c) first derivative of curve b.



The simvastatin-SDS interaction was different to that seen for SDCH. Here the cmc was shifted from 8.2mM in water to 7.6mM, which shows an increased driving force to form the micelle in the presence of drug. This is in keeping with the solubility data which showed that each micelle would solubilise 20 simvastatin molecules. In this instance any enhancement of absorption would be a consequence of the solubilisation and the stabilisation of the SDS micelle.

Much remains to be understood about how drug-surfactant interactions can result in changes in drug absorption. We believe that advances in the understanding of these complex interactions will be achieved through fundamental studies of drug-surfactant interaction such as those reported here. Based on the findings that simvastatin interacts very differently with these two surfactants it may be possible to study, and then understand, the impact which these surfactants have on drug absorption.